Table 13: Subdomains of SF-36

	Actual Mean (Median) Values		Change from Baseline		
Component *	Placebo N = 104 mean (median)	Etanercept N = 101 mean (median)	Placebo N = 104 mean (median)	Etanercept N = 101 mean (median)	p value**
Physical functioning					
Baseline	37.1 (36.2)	35.9 (36.2)			
24 weeks	38.0 (38.3)	44.4 (48.8)	0.9 (0)	8.5 (8.4)	< 0.001
Physical role					
Baseline	38.4 (35.0)	40.8 (42.1)			
24 weeks	37.8 (28.0)	47.8 (56.2)	-0.5 (0)	6.9 (7.1)	< 0.001
Bodily pain					
Baseline	38.6 (37.5)	38.6 (37.5)			
24 weeks	40.1 (37.9)	48.5 (51.6)	1.5 (0)	9.9 (9.4)	< 0.001
General health					
Baseline	40.0 (39.2)	42.3 (41.5)			
24 weeks	39.7 (39.2)	47.3 (46.2)	-0.4 (0)	5.0 (4.7)	< 0.001
Vitality					
Baseline	41.8 (42.0)	43.6 (44.3)			
24 weeks	43.1 (44.3)	50.9 (51.4)	1.3 (0)	7.3 (7.1)	< 0.001
Social functioning					
Baseline	43.1 (46.3)	44.0 (46.3)			
24 weeks	43.7 (46.3)	50.8 (57.1)	0.6 (0)	6.8 (5.4)	< 0.001
Emotional role					
Baseline	43.7 (55.3)	47.6 (55.3)			
24 weeks	43.0 (55.3)	51.0 (55.3)	-0.7 (0)	3.3 (0)	0.073
Mental health					
Baseline	48.5 (50.4)	48.8 (50.4)			
24 weeks	48.6 (50.4)	51.9 (52.7)	0.1 (0)	3.2 (2.3)	0.001

* 0 = worst; 100 = best; 50 = U.S. norm

** p values determined by 2-sided Wilcoxon rank sum test

3. *Psoriasis endpoints*

Assessment of psoriasis was a secondary endpoint in study 16.0030. All subjects were assessed for response of their target lesion, which was defined as a lesion of 2 cm diameter or greater that was stable at baseline. In addition, patients with psoriasis involvement of at least 3% of their body surface area (BSA) were assessed for their Psoriasis Area and Severity Index (PASI) scores. Last observation carried forward (LOCF) was used to impute missing values. As shown in Table 14, no major imbalances were seen between the two study arms with respect to the duration of psoriasis, the extent of disease at baseline or concomitant use of corticosteroids or MTX. Improvement in the target lesions was seen as early as 4 weeks in etanercept-treated patients (Table 15). The

improvement seen in target lesions reached 33% at 3 months and was similar at 6 months. The unadjusted p values for the comparisons with placebo were <0.001 at each time point. A higher proportion of patients experienced large levels of improvement in their target lesions with etanercept than with control, with 43% of patients achieving a 50% improvement and 22% a 75% improvement. Approximately 10% of patients had a 90% improvement in target lesions, which was not significantly different from controls.

All patients were also assessed using the Dermatologist Static Global Assessment of Target Lesions. A total of 40/101, or 40% of etanercept-treated patients had a reduction in target lesions to completely clear or almost clear, compared to 20% of placebo-treated patients. Fifty-five percent (55/101) of etanercept-treated patients had improvement in their Dermatologist Static Global Assessment of Psoriasis to clear or minimal, compared to 23% of patients receiving placebo.

Table 14: Baseline Psoriasis Activity

	Placebo	**Etanercept**
Characteristic	N = 104	N = 101
Duration of PsA in years (mean)	9.2	9.0
Duration of psoriasis in years (mean)	19.7	18.3
Mean psoriasis BSA (%)	10.2	10.9
(range)	(1.0 – 90.0)	(0.5 – 80.0)
Target lesion score at baseline (mean [median])*	5.4 (5.0)	5.4 (6.0)
Dermatologist target lesion assessment at baseline (n [%]):		
Almost clear	5 (5)	3 (3)
Mild	43 (41)	36 (36)
Moderate	43 (41)	56 (55)
Severe	12 (12)	6 (6)
Very severe	1 (1)	0 (0)
Patients evaluable for PASI (n [%])	62 (60)	66 (65)
No. of prior DMARDs (mean)	1.6	1.7
Concomitant therapy during study (n [%]):		
Corticosteroids	16 (15)	19 (19)
NSAIDs	86 (83)	89 (88)
Methotrexate	43 (41)	42 (42)

* Scale: 0- none, 12 = very severe

Table 15: Response of Psoriasis Target Lesions

	Placebo		Etanercept		
Parameter	N = 104		N = 101		p value
Target lesion score (mean [median]): *					
Baseline	5.4 (5.0)		5.4 (6.0)		
4 weeks	4.8 (5.0)		3.9 (3.0)		
12 weeks	4.5 (5.0)		3.4 (3.0)		
24 weeks	4.8 (5.0)		3.2 (3.0)		
Percent improvement from baseline (mean [median]):					
4 weeks	8.3 (0)		25.7 (28.6)		< 0.001 **
12 weeks	15.3 (0)		31.6 (33.3)		< 0.001 **
24 weeks	10.8 (0)		35.6 (33.3)		< 0.001 **
Target lesions at 24 weeks – improved by (number [%]):					
50%	18 (17)		43 (43)		< 0.001 ***
75%	10 (10)		22 (22)		0.017 ***
90%	8 (8)		13 (13)		0.224 ***
Dermatologist Static Global Assessment of Target Lesions (number [%]):	Baseline	24 Wks	Baseline	24 Wks	< 0.001 ***
Completely clear	0	9 (9)	0	18 (18)	
Almost clear	5 (5)	11 (11)	3 (3)	22 (22)	
Mild	43 (41)	34 (33)	36 (36)	39 (39)	
Moderate	43 (41)	37 (36)	56 (55)	20 (20)	
Severe	12 (12)	12 (12)	6 (6)	2 (2)	
Very severe	1 (1)	1 (1)	0	0	
Dermatologist Static Global Assessment of Psoriasis (number [%]):	Baseline	24 Wks	Baseline	24 Wks	< 0.001 ***
Clear	0	6 (6)	0	14 (14)	
Minimal	21 (20)	18 (17)	20 (20)	41 (41)	
Mild	35 (34)	34 (33)	39 (39)	25 (25)	
Moderate	42 (40)	34 (33)	35 (35)	20 (20)	
Marked	5 (5)	11 (11)	7 (7)	1 (1)	
Severe	1 (1)	1 (1)	0	0	

* Scale: 0 = none, 12 = very severe

** p values determined by 2-sided Wilcoxon rank sum test

*** p values determined by Cochran-Mantel-Haenszel row means test, treatment comparison at week 24

PASI scores were assessed in the subset of patients with at least 3% BSA involved with psoriasis. All subjects in this subgroup completed 12 weeks of assessments on study and over 95 percent of subjects completed 12 weeks on study drug (Table 16). Also, over 90% of subjects in each study arm completed 6 months on study. While 95% of subjects completed 6 months on study drug, only 71% of subjects in the placebo arm did. The reason for the difference is largely accounted for by 13 patients (13/62, or 21%) in the placebo arm who dropped out for lack of efficacy with respect to their arthritis, compared to a single patient in the etanercept arm. No major imbalances in baseline characteristics were observed between the two study arms in the predefined subset for assessing PASI scores.

A greater degree of improvement was seen in the PASI scores of the etanercept-treated patients than the controls (Table 18). The mean improvement among etanercept-treated patients was 41% at 3 months and 47% at 6 months, compared to 3% and –8% for controls (unadjusted p values for both comparisons <0.001). More patients in the etanercept arm experienced 75% or greater improvement in PASI scores at 6 months (23% vs. 3%, unadjusted p value = 0.001. Forty-seven percent of etanercept-treated patients had improvement in the Dermatologist Static Global Assessment of Psoriasis to clear or minimal, compared to 11% of placebo-treated patients. Finally, more etanercept-treated patients experienced a 75% or greater improvement in PASI scores at 6 months in the subset of patients who began the study with at least 10% BSA involved with psoriasis (Table 19).

Table 16: Prespecified Subset for Evaluation of PASI Responses: Patient Disposition

	Placebo	**Etanercept**
	(N = 62)	(N = 66)
Status	n (%)	n (%)
Completed 12 weeks in study	62 (100)	66 (100)
Completed 12 weeks on study drug	60 (97)	65 (98)
Discontinued study drug for:		
Lack of efficacy (LOE)	1 (2)	0
Lost to follow-up	1 (2)	1 (2)
Completed 24 weeks in study	56 (90)	64 (97)
Completed 24 weeks on study drug	44 (71)	63 (95)
Discontinued study drug for:		
Death	1 (2)	0
Adverse event	1 (2)	0
Lack of efficacy (LOE)	13 (21)	1 (2)
Lost to follow-up	2 (3)	1 (2)
Patient refusal	1 (2)	1 (2)

Table 17: Prespecified Subset for Evaluation of PASI Responses: Baseline Characteristics

	Placebo	Etanercept
Characteristic	N = 62	N = 66
Mean age in years	46.8	45.8
(range)	(21 – 69)	(18 – 72)
Male (n [%])	31 (50)	37 (56)
Race (n [%]):		
Caucasian	56 (90)	61 (92)
Hispanic	2 (3)	2 (3)
Black	2 (3)	2 (3)
Other	2 (3)	1 (2)
Mean weight (kg)	89.5	91.2
Duration of psoriasis in years (mean)	20.6	19.3
Mean psoriasis BSA (%)	16.0	15.8
(range)	(3 – 90)	(3 – 80)
PASI score at baseline (mean) *	11.1	9.6
Concomitant methotrexate during study (n [%])	29 (47)	28 (42)

* Scale = 0-72

Table 18: PASI Score Responses

	Placebo		Etanercept		
Parameter	N = 62		N = 66		p value
PASI: Percent improvement from baseline (mean [median]):					
4 weeks	1.4 (0)		21.2 (24.6)		< 0.001 *
12 weeks	3.1 (7.3)		38.1 (40.6)		< 0.001 *
24 weeks	-8.1 (0)		42.0 (47.1)		< 0.001 *
PASI score at 24 weeks – improved by (n [%]):					
50%	11 (18)		31 (47)		< 0.001 **
75%	2 (3)		15 (23)		0.001 **
90%	2 (3)		4 (6)		0.681 ***
Dermatologist Static Global Assessment of Psoriasis at 24 weeks (n [%]):	Baseline	24 Wks	Baseline	24 Wks	< 0.001 **
Clear	0	2 (3)	0	7 (11)	
Minimal	5 (8)	5 (8)	5 (8)	24 (36)	
Mild	20 (32)	19 (31)	24 (36)	20 (30)	
Moderate	31 (50)	26 (42)	30 (45)	15 (23)	
Marked	5 (8)	9 (15)	7 (11)	0	
Severe	1 (2)	1 (2)	0	0	

* p values determined by 2-sided Wilcoxon rank sum test

** p values determined by Cochran-Mantel-Haenszel row means test, treatment comparison at week 24

*** p values determined by Fisher's exact test

Table 19: PASI Score Responses in Subset with ≥10% BSA Psoriasis Involvement

PASI score at 24 weeks – improved by (number [%]):	Placebo N = 29	Etanercept N = 33	P value
50%	5 (17)	18 (55)	0.003 *
75%	1 (3)	10 (30)	0.007 **
90%	1 (3)	2 (6)	1.000 **

* p values determined by Cochran-Mantel-Haenszel row means test, treatment comparison at week 24

** p values determined by Fisher's exact test

The agency performed an exploratory analysis to examine the relationship between the improvement in peripheral arthritis and in psoriasis observed in the etanercept-treated group. The analysis was carried out to ask to what extent improvement in PASI scores could be explained by the improvement in arthritis. As shown in Table 20, the 11 of 62 or 18% of placebo-treated patients who had an ACR20 response experienced a higher degree of improvement in their PASI scores than placebo-treated patients who did not have an ACR20 response, although the differences were not statistically significant. Etanercept-treated patients who did not have an ACR20 response also had a smaller degree of improvement in the PASI scores (23% vs. 48%) than those who did (unadjusted $p < 0.05$). Of note, the improvement in PASI scores seen in the etanercept-treated patients who did not have an ACR20 response was higher than that seen in placebo-treated patients who did have an ACR20 response. These data suggest that not all the improvement in PASI scores can be explained by improvement in arthritis.

Table 20: Percent Improvement in PASI Scores from Baseline at 12 Weeks in Patients Subsetted by ACR20 Response

Treatment	ACR20	N	Mean	Median	P values
Placebo	N	51	1.76	0	P = 0.78
"	Y	11	9.12	12.9	
Etanercept	N	26	23.4	31.8	P = 0.0002
"	Y	40	47.7	43.8	

III. Study 16.0612

This was a double-blind, randomized, 60-patient, single-center, phase 2 trial comparing etanercept 25 mg biw sc with placebo, conducted by a sponsor-investigator. Patients

were enrolled who had active psoriatic arthritis, as defined by at least 3 swollen and at least 3 tender/painful joints and an inadequate response to NSAID therapy. Patients previously receiving MTX were allowed to remain on a stable dose of MTX up to 25 mg/week, but other DMARDs were not allowed. Stable NSAIDs and corticosteroids up to prednisone 10 mg/d or its equivalent were allowed. Patients were required to be considered a suitable candidate for immunomodulatory therapy or, if not, that they had psoriasis involvement of at least 10% BSA and had failed one form of systemic therapy. A prespecified subgroup was evaluated for the response of their psoriasis to therapy, defined as patients with stable plaque psoriasis with at least 3% of body surface area involved and an inadequate response to topical therapy. Ultraviolet treatment was not allowed during the study or within 1 month of beginning study drug treatment. The use of tar compounds and steroid-free topical emollients was allowed, but topical steroid creams, lotions or other preparations (vitamins A or D, Anthralin compounds) were not allowed.

The primary endpoint for psoriatic arthritis was the proportion of patients responding at 12 weeks as defined by improvement in at least 2 of the 4 measures of a modified form of the PsA Response Criteria (PsARC), one of which had to be tender or swollen joint scores and with no worsening in any measure. The ACR20 was added as a secondary endpoint during the trial. The PsARC criteria used were:

- Patient global assessment, measured on a 6-point Likert scale. Improvement defined as a decrease of 1 or more; worsening defined as increase of 1 or more;
- M.D. global assessment, measured on a 6-point Likert scale. Improvement defined as a decrease of 1 or more; worsening defined as increase of 1 or more;
- Tender/painful joint scores based on examination of 78 joints on a 4-point scale with 0=none to 3=severe. Improvement defined as decrease by 30% or more; worsening defined as increase of 30% or more;
- Swollen joint scores based on examination of 76 joints on a 4-point scale with 0=none to 3=severe. Improvement defined as decrease by 30% or more; worsening defined as increase of 30% or more

The primary psoriasis endpoint was the proportion of patients with at least 75% improvement in PASI score at 12 weeks in the predefined subset. A secondary psoriasis endpoint was assessment of an individual target lesion. The primary analysis of the response rates specified use of the Cochran-Mantel-Haenszel chi-square test stratified for MTX use.

A. Study conduct

A total of 60 patients were randomized (Table 21). All patients completed 12 weeks of blinded study drug in the etanercept group and 87% in the placebo group. Overall, the two study arms were reasonably well balanced with respect to baseline demographics (Table 22) and baseline disease activity (Table 23), except that a higher proportion of

patients in the placebo arm were on baseline corticosteroids compared to the etanercept arm. Patients enrolled in the study had long-standing, active psoriatic arthritis.

Table 21: Study 0612: Patient Disposition

	Placebo	**Etanercept**
	(N = 30)	(N = 30)
Status	n (%)	n (%)
Completed	26 (87)	30 (100)
Discontinued:		
Lack of efficacy (LOE)	2 (7)*	0
Lost to follow-up	1 (3)	0
Patient refusal	1 (3)	0

Table 22: Study 0612: Baseline Demographics

	Placebo	**Etanercept**
Characteristic	N = 30	N = 30
Median age (years)	43.5	46.0
Male (n [%])	18 (60)	16 (53)
Caucasian (n [%])	25 (83)	27 (90)
Median weight (kg)	82.3	90.7
Duration of PsA in years (median)	9.5	9.0
Duration of psoriasis in years (median)	17.5	19.0
No. of prior DMARDs (median)	2.0	1.5
Concomitant therapy during study (n [%]):		
Corticosteroids	12 (40)	6 (20)
NSAIDs	23 (77)	20 (67)
Methotrexate	14 (47)	14 (47)

Table 23: Study 0612: Baseline Disease Activity

	Placebo	**Etanercept**
	N = 30	N = 30
Status	Mean (median)	mean (median)
Tender joint count [a]	25.3 (19.0)	22.7 (22.5)
Tender joint score [b]	36.0 (21.4)	27.9 (25.8)
Swollen joint count [c]	18.3 (14.7)	15.7 (14.0)
Swollen joint score [d]	23.3 (19.8)	19.8 (17.5)
Physician global assessment [e]	3.4 (3.0)	3.3 (3.0)
Patient global assessment [e]	2.9 (3.0)	3.3 (3.0)
Morning stiffness (minutes)	59.7 (60.0)	56.5 (60.0)
Pain assessment [e]	3.1 (3.0)	3.0 (3.0)
Quality of life (HAQ) [f]	1.2 (1.2)	1.2 (1.3)
ESR [g]	23.2 (16.0)	26.6 (22.0)
CRP [h]	1.6 (1.2)	2.3 (1.4)

a Scale 0 – 78
b Sum of 78 joint pain/tenderness scores measured on a 4-point scale
c Scale 0 – 76
d Sum of 76 joint swelling scores measured on a 4-point scale
e 0 = best, 5 = worst (Likert scale)
f 0 = best, 3 = worst
g Normal range: 1 – 13 mm/hr for men; 1 – 30 mm/hr for women
h Normal range: 0 – 1.00 mg/dL

B. Efficacy analysis

As stated above, the primary endpoint with respect to psoriatic arthritis was the proportion of patients achieving a response based on the PsARC at 12 weeks (Table 24). Eighty-seven percent of etanercept-treated patients achieved a response based on the PsARC, as compared to 23% of patients receiving placebo. Signs and symptoms of psoriatic arthritis, as measured by the PsARC, were improved as early as 4 weeks and responses were maintained to 3 months. Improvement in the ACR response criteria was also observed (Table 25). Seventy-three percent of etanercept-treated subjects achieved an ACR20 response at 12 weeks and 50% achieved an ACR 50 response. Of note, the proportion of subjects receiving placebo who met response criteria was lower using the ACR20 (13%) than with the PsARC (23%). The proportion meeting response criteria in the etanercept group was also somewhat lower using ACR criteria than with the PsARC. Treatment with etanercept was associated with improvement in each of the components of the ACR response criteria (Table 26).

Table 24: Study 0612: Primary Psoriatic Arthritis Endpoint

	Placebo	Etanercept	
	N = 30	N = 30	
Achieved PsARC	n (%)	n (%)	p value*
4 weeks	4 (13)	23 (77)	< 0.001
8 weeks	8 (27)	25 (83)	< 0.001
12 weeks	7 (23)	26 (87)	< 0.001

* Determined by CMH chi-square test

Table 25: Study 0612: Patients Attaining ACR 20/50/70 Responses

	Placebo	Etanercept	
	N = 30	N = 30	
Parameter	n (%)	n (%)	p value*
ACR 20			
4 weeks**	1 (3)	18 (60)	< 0.001
8 weeks**	3 (10)	19 (63)	< 0.001
12 weeks	4 (13)	22 (73)	< 0.001
ACR 50			
4 weeks**	0	6 (20)	0.024 ‡
8 weeks**	1 (3)	11 (37)	0.001
12 weeks	1 (3)	15 (50)	< 0.001
ACR 70			
4 weeks**	0	1 (3)	NS
8 weeks**	0	5 (17)	NS
12 weeks	0	4 (13)	NS

* p values determined by CMH chi-square test

** Because ESR and CRP (acute phase reactants) were only assessed at baseline and 12 weeks, improvement at the 4- and 8-week timepoints were required in 3 of 4 secondary parameters instead of 3 of 5 parameters.

‡ p value determined by Fisher's exact test

NS Not significant by Fisher's exact test

Table 26: Study 0612: Components of ACR20

	Placebo	**Etanercept**
	N = 30	N = 30
Parameter	mean (median)	mean (median)
Tender joint count: [a]		
Baseline	25.3 (19.0)	22.7 (22.5)
4 weeks	25.7 (19.5)	13.0 (11.0)
8 weeks	26.2 (21.5)	11.4 (7.5)
12 weeks	29.7 (22.5)	8.5 (6.0)
Swollen joint count: [b]		
Baseline	18.3 (14.7)	15.7 (14.0)
4 weeks	16.9 (13.0)	9.1 (7.5)
8 weeks	15.1 (9.0)	5.7 (3.0)
12 weeks	16.3 (11.0)	5.1 (3.0)
Physician global assessment: [c]		
Baseline	3.4 (3.0)	3.3 (3.0)
4 weeks	3.3 (3.0)	2.0 (2.0)
8 weeks	3.1 (3.0)	1.5 (1.0)
12 weeks	3.1 (3.0)	1.2 (1.0)
Patient global assessment: [c]		
Baseline	2.9 (3.0)	3.3 (3.0)
4 weeks	3.0 (3.0)	2.2 (2.0)
8 weeks	2.8 (3.0)	1.7 (2.0)
12 weeks	2.9 (3.0)	1.3 (1.0)
Morning stiffness (minutes):		
Baseline	59.7 (60.0)	56.5 (60.0)
4 weeks	54.8 (60.0)	29.5 (30.0)
8 weeks	52.8 (60.0)	26.5 (17.5)
12 weeks	61.8 (60.0)	20.7 (5.0)
Pain assessment: [c]		
Baseline	3.1 (3.0)	3.0 (3.0)
4 weeks	2.8 (3.0)	1.8 (2.0)
8 weeks	2.8 (3.0)	1.5 (2.0)
12 weeks	2.9 (3.0)	1.4 (1.0)
ESR: [d] *		
Baseline	23.2 (16.0)	26.6 (22.0)
12 weeks	24.4 (19.0)	11.1 (5.0)
CRP" [e] *		
Baseline	1.6 (1.2)	2.3 (1.4)
12 weeks	2.0 (1.5)	0.8 (0.4)

* ESR and CRP (acute phase reactants) were only assessed at baseline and 12 weeks.
a Scale 0 – 78 d Normal range: 1 – 13 mm/hr for men;
b Scale 0 – 76 1 – 30 mm/hr for women
c 0 = best, 5 = worst (Likert scale) e Normal range: 0 – 1.00 mg/dL

In study 0612, patients were stratified based on whether they were or were not receiving MTX at baseline and during the trial. Higher response rates at 12 weeks were seen in the

etanercept-treated group than placebo for the subset who was receiving concomitant MTX as well as for the group that was not (Table 27). Another background medication that could influence response rates in the trial is corticosteroid use. As noted above, the two treatment arms were unbalanced with respect to background corticosteroid use, with twice as many placebo patients as etanercept-treated patients receiving corticosteroids. As shown in Table 28, corticosteroid use did not influence the likelihood of response in either the etanercept group or control. Use of etanercept was associated with higher rates of response in corticosteroids users and non-users.

Table 27: Study 0612: PsARC Responses in Patients Subsetted on Concomitant MTX Use

	MTX		Non-MTX	
	Placebo N = 14	Etanercept N = 14	Placebo N = 16	Etanercept N = 16
Achieved PsARC Timepoint:	n (%)	n (%)	n (%)	n (%)
4 weeks	4 (29)	12 (86)*	0	11 (69)*
8 weeks	5 (36)	12 (86)*	3 (19)	13 (81)*
12 weeks	3 (21)	13 (93)*	4 (25)	13 (81)*

* p values < 0.05 for all comparisons (CMH chi-square test)

Table 28: Study 0612: PsARC Responses in Patients Subsetted on Concomitant Corticosteroid Use

	Corticosteroid Users		Non-Corticosteroid Users	
	Placebo N = 12	Etanercept N = 6	Placebo N = 18	Etanercept N = 24
Achieved PsARC Timepoint:	n (%)	N (%)	n (%)	n (%)
12 weeks	3 (25)	5 (83)*	4 (22)	21 (88)*

* p values < 0.05 for all comparisons (CMH chi-square test)

1.2 *Psoriasis endpoints*

Of the 60 patients in study 0612, 38 had evaluable psoriasis, 19 in each treatment group. All patients in the etanercept group completed the 12-week study, while 3 patients in the placebo group discontinued prematurely, 2 for lack of efficacy and one for loss to follow-up. The baseline demographics were reasonably well balanced across study arms with the exception of psoriasis involvement, which was higher in etanercept-treated patients, and corticosteroid use, which was considerably more common among those receiving placebo (Table 29).

Table 29: Study 0612: Baseline Demographics: Psoriasis

	Placebo	**Etanercept**
Characteristic	N = 19	N = 19
Median age (years)	44.0	44.0
Male (n [%])	10 (53)	11 (58)
Caucasian (n [%])	16 (84)	17 (89)
Median weight (kg)	83.0	94.8
Duration of psoriasis in years (median)	20.0	20.0
Psoriasis involvement (PASI) (median) [a]	6.0	10.1
Target lesion assessment (median) [b]	6.0	6.0
No. prior DMARDs (median)	2.0	2.0
No. on methotrexate (%)	10 (53)	8 (42)
Concomitant therapy during study (n [%]):		
Corticosteroids	8 (42)	2 (11)
NSAIDs	15 (79)	15 (79)

a Scale = 0 – 72
b Scale = 0 – 12

The primary efficacy endpoint for psoriasis was the proportion of subjects who had improvement in PASI scores of 75% or more. As shown in Table 30, 26% of etanercept-treated patients attained a 75% improvement in PASI scores, compared to none of the placebo-treated group. More patients in the etanercept group had 25% and 50% improvement in their target lesions at 12 weeks, but only 2 of the etanercept-treated group had 75% improvement in their target lesion, which was not significantly different from the rate among controls. The median percent improvement in both the PASI scores and the target lesion responses were both higher in etanercept-treated patients.

Table 30: Study 0612: Psoriasis Efficacy Results

	Placebo	Etanercept	p value
Parameter	N = 19 n (%)	N = 19 n (%)	Placebo vs. Etanercept
PASI ▯ improved by:			
25%	8 (42)	14 (74)	0.099 *
50%	4 (21)	8 (42)	0.295 *
75%	0	5 (26)	0.046 *
Target lesions ▯ improved by:			
25%	6 (32)	14 (74)	0.022 *
50%	2 (11)	12 (63)	0.002 *
75%	0	2 (11)	0.486 *
Target lesion response rate:			0.001 †
Worsened	1 (5)	0	
No change	12 (63)	5 (26)	
25% improvement	4 (21)	2 (11)	
50% improvement	2 (11)	10 (53)	
75% improvement	0	0	
Completely cleared	0	2 (11)	
Median % improvement:			
PASI score	8.8	46.2	0.003 ‡
Target lesions	0	50.0	< 0.001 ‡

* p values determined by Fisher's exact test
† p value for Week 12 overall; determined by CMH chi-square test
‡ p values determined by ANOVA on ranked data

C. Safety

1. *Deaths and serious adverse events*

In the pivotal trial (16.0030), there were no deaths in the etanercept group. One death occurred in the placebo group. Eight serious adverse events (SAE's) occurred in the trial: 4 in placebo recipients; 4 in 4 etanercept-treated patients. The SAE's seen among etanercept-treated patients were: non-cardiac chest pain; renal calculus; multiple sclerosis (MS) and syncope. The patients with MS was a 38 year old man with no history of neurologic disease. After 113 days on study drug, he reported tingling sensations in both feet, followed by numbness of both palms. An MRI of the brain showed multifocal white matter changes in the brain and cervical spinal cord. Spinal tap showed slightly elevated CSF protein. He continued on the study through 24 weeks, but did not continue to maintenance.

No SAEs were observed during the 12-week blinded portion of study 0612 or in the 30-day follow-up period. However, one SAE was observed in the 24-week extension study. On day 236, patient no. 26 developed tingling in both hands that was diagnosed as MS.

The investigator consider the event to be unrelated to etanercept and the patient continued on etanercept therapy.

2. *Discontinuations due to toxicity*

One patient in the placebo group and one in the etanercept group discontinued study drug due to toxicity in study 0030. The patient receiving placebo discontinued due to increased psoriasis. The patient receiving etanercept was receiving concomitant MTX. He discontinued due to liver function abnormalities.

3. *Laboratory abnormalities*

No pattern of abnormal laboratory values was noted among the etanercept-treated patients in study 0030.

4. *Response to Vaccination*

In study 0030, all patients received pneumococcal polysaccharide vaccination at week 4. Serum samples were obtained prior to vaccination and 4 weeks later. IgG antibodies to 5 pneumococcal polysaccharide antigens were measured by [redacted] Paired specimens were available from 90 placebo-treated and 94 etanercept-treated patients. The sponsor's primary analysis of the vaccination data was a calculation of the proportion of subjects who had at least a 2-fold increase in titers to 2, 3, 4 or 5 antigens. As shown in Table 31, a similar proportion of patients in the etanercept and placebo groups had an increase in titer to 2, 3, 4 or 5 antigens. When examined by the individual pneumococcal antigens (Table 32), similar proportions of patients had at least a 2-fold increase in titer to each of the 5 antigens examined. However, for each antigen, the proportion of etanercept-treated patients with a ≥ 2-fold increase in titer was the same or slightly less than placebo-treated patients, suggesting that responses to pneumococcal vaccination might be slightly lower in those receiving etanercept.

Table 31: Number of patients with at Least a 2-Fold Increase in Pneumococcal Antibody Titers

	Placebo	**Etanercept**
Number of antigens with ≥ 2-fold increase in titers	N = 90 N (%)	N = 94 n (%)
2	24 (27)	23 (24)
3	5 (6)	17 (18)
4	23 (26)	20 (21)
5	38 (42)	34 (36)
Mean (median) number of antigens with 2-fold increase	3.8 (4.0)	3.7 (4.0)

Table 32: Number (%) of Patients with at Least a 2-Fold Increase in Pneumococcal Titers, by Antigen

	Placebo	Etanercept
	N = 90	N = 94
Pneumococcal antigen	n (%)	n (%)
9V	53 (59)	47 (50)
14	56 (62)	55 (59)
18C	56 (62)	58 (62)
19F	36 (40)	33 (35)
23F	52 (58)	48 (51)

To further investigate the responses to pneumococcal vaccination among etanercept recipients and controls, the agency examined geometric mean titers. As shown in Table 33, geometric mean titers were lower in etanercept-treated patients than controls for each of the 5 antigens tested. The ratios ranged from approximately 0.6 to 0.8. In each case except antigen 14, the 95% confidence interval overlapped 1. Thus geometric mean titers appear to be slightly lower with etanercept than control in a systematic fashion.

Table 33: Geometric Mean Titers 4 Weeks Post-Vaccination

	Geometric Mean Titer		Ratio	Two-Sided 95% CI for Ratio	
Antigens	Placebo	Etanercept	(Etanercept/Placebo)	Lower CI	Upper CI
9V	5.9353	4.4852	0.7557	0.5238	1.0902
14	33.4221	18.7943	0.5623	0.3581	0.8829
18C	7.9384	6.1851	0.7791	0.5365	1.1314
19F	14.1723	11.8809	0.8383	0.6153	1.1421
23F	4.9960	4.1605	0.8328	0.5537	1.2526

Other factors besides use of etanercept may have influenced the responses of the patients in study 0030 to vaccination, including concomitant medications. The sponsor carried out a number of analyses to assess the effect of concomitant use of methotrexate, corticosteroids and of baseline demographic factors. As shown in Table 34, patients receiving concomitant corticosteroids appeared to respond similarly as those not receiving corticosteroids, as assessed by the proportion of subjects who developed at least a 2-fold increase in titer to the five antigens tested. In contrast, patients receiving concomitant methotrexate were consistently 30-50% less likely to respond to pneumococcal antigens.

A univariate analysis was carried out to assess the effects of other baseline variables on antibody responses to pneumococcal polysaccharide. Patients were categorized as having a poor response if they responded to 2 or 3 of the 5 pneumococcal antigens tested (38% of all patients) and as having a good response if they responded to 4 or 5 antigens (62% of patients). The variables tested included age, gender, therapies (etanercept, methotrexate and oral corticosteroids), co-morbidities (diabetes and COPD) and CRP. The variables that were associated with a higher risk of a poor response to vaccination

(Table 35) were, in order of risk, MTX use, concomitant diabetes, age over 40, female gender and etanercept use.

A logistic regression analysis was used to explore potential interactions between variables. The candidates were as listed above for the univariate analysis, except that age was divided into age groups of 18-40, 41-65 and 65 and older. Candidates were selected and eliminated using a p value cutoff of < 0.10. To determine the most important variables apart from treatment arm, etanercept treatment was excluded as a variable. The final model included the variables MTX use, older age groups and diabetes (Table 36) as predictors of a poor response. There was no interaction between any of the covariates and etanercept treatment ($p>0.2$) or with MTX use ($P>0.02$) and no interaction between etanercept treatment and MTX use ($P=0.61$). Testing etanercept treatment in this model produced a p value of 0.1049.

To assess directly whether there was an interaction between MTX use and etanercept treatment, responses to each of the pneumococcal polysaccharide antigens were determined. As shown in Table 37, the proportion of subjects with a 2-fold or greater response was lower for each of the 5 antigens for patients taking concomitant MTX than those not receiving MTX. Concomitant MTX use was associated with lower titers among patients in both the etanercept arm and the control arm. The degree to which titers were lower among patients with concomitant MTX use did not appear to be any greater for patients in the etanercept arm than for patients receiving placebo. These data do not indicate that there is an interaction between etanercept and MTX with respect to responses to pneumococcal vaccination.

Table 34: Response to Pneumococcal Vaccine (≥2-Fold Increase), Subsetted by Concomitant Methotrexate and Corticosteroid Use

	Methotrexate		Corticosteroids	
Pneumococcal Antigen	No (n=104)	Yes (n=80)	No (n=162)	Yes (n=22)
9V	69	35	52	68
14	77	39	60	64
18C	75	45	60	73
19F	44	29	38	36
23F	67	38	53	64

Table 35: Univariate Analysis: Relative Risk for Poor Response to Pneumococcal Vaccination

	P-Value*	Relative Risk	95% CI
MTX Use = Yes	<.0001	2.131	1.601-2.838
Age (>40)	0.0002	1.542	1.267-1.877
Gender (Female)	0.0681	1.235	0.981-1.554
Corticosteroids Use=Yes	0.1282	0.783	0.605-1.014
Diabetes=Yes	0.1318	1.595	0.740-3.435
Etanercept=Yes	0.1490	1.180	0.942-1.477
Pulmonary Disease=Yes	0.5745	0.903	0.651-1.254
Elevated CRP (>0.8)	0.8774	0.982	0.782-1.234

* Mantel - Haenszel Row Mean Test. P value uncorrected for multiple comparisons

Table 36: Logistic Regression: Relative Risk for Poor Response to Pneumococcal Vaccination

	Relative Risk	95% CI
MTX Use = Yes	3.67	2.70-4.51
Age (> 65)	4.51	2.08-5.86
Age (41-65)	2.85	1.60-4.32
Diabetes = Yes	1.84	0.89-2.49

Table 37: Subjects with at least 2-fold rise in titer subsetted by MTX use

Antigen	Analysis Subset	Placebo	**Etanercept**
A9V	MTX user	17/42 (40%)	10/41 (24%)
	Non-MTX user	36/48 (75%)	37/53 (70%)
A14	MTX user	16/42 (38%)	15/41 (37%)
	Non-MTX user	40/48 (83%)	40/53 (75%)
A18C	MTX user	20/42 (48%)	15/41 (37%)
	Non-MTX user	36/48 (75%)	43/53 (81%)
A19F	MTX user	11/42 (26%)	11/41 (27%)
	Non-MTX user	25/48 (52%)	22/53 (42%)
A23F	MTX user	17/42 (40%)	12/41 (29%)
	Non-MTX user	35/48 (73%)	36/53 (68%)

5. *Other adverse events*

Injection site reactions were observed in 36% of etanercept-treated patients, compared to 9% of those receiving placebo. This rate is similar to that seen in other trials of etanercept. All injection site reactions were grade 1 or 2. Adverse events were observed in a similar proportion of patients in both treatment groups. Apart from injection site

reactions, no other adverse events showed a pattern of occurring at a higher rate in etanercept-treated patients.

Table 38: Study 16.0030: Adverse Events Occurring in 5% or more of Patients

	Placebo	**Etanercept**
	N = 104	N = 101
Event	n (%)	n (%)
Any adverse event	69 (66)	65 (64)
Injection site reaction	9 (9)	36 (36)
Injection site ecchymosis	11 (11)	12 (12)
Accidental injury	5 (5)	8 (8)
Headache	5 (5)	8 (8)
Rash	7 (7)	5 (5)
Cough increase	6 (6)	4 (4)
Dizziness	5 (5)	4 (4)
Nausea	7 (7)	2 (2)
Rhinitis	7 (7)	1 (1)
Diarrhea	6 (6)	1 (1)
Dyspepsia	6 (6)	1 (1)
Immunization reaction	6 (6)	0
Pruritus	5 (5)	1 (1)

IV. Summary of efficacy

Etanercept demonstrated efficacy in a randomized, placebo-controlled, multi-center trial in psoriatic arthritis as measured by a decrease in the ACR20 at 12 and 24 weeks. The proportion of subjects with higher levels of response, i.e. ACR 50 and 70, was also increased. Decreases in each of the components of the ACR20 were also observed, including tender and swollen joint counts, patient and physician global assessment, assessment of pain, disability and acute phase reactants. The results indicate that the effects of etanercept on peripheral arthritis are observed in all subtypes of psoriatic arthritis. Similar benefits were observed in etanercept-treated patients subsetted on differing baseline demographic features and on baseline disease activity and duration. Similar responses were seen in patients who were and those who were not taking methotrexate at baseline.

Improvements in psoriasis were also observed in psoriatic arthritis patients treated with etanercept. Decreases in target lesion scores were observed at 12 and 24 weeks. In addition, in the prespecified subset of patients with at least 3% of body surface area

involved with psoriasis, there was an increase in the proportion of patients with 50% and 75% improvement in PASI scores.

Similar results were seen in a 60-patient, randomized, placebo-controlled, single center phase 2 study with respect to improvement in active arthritis and in psoriasis.

V. Summary of safety

No deaths were observed among etanercept-treated patients with psoriatic arthritis. One case of multiple sclerosis (MS) was observed in the phase 3 study, manifest by tingling sensations in the feet and numbness of the palms and one case of MS was observed in the uncontrolled, long-term extension phase of study 0612, manifested by tingling in the hands. Cases of new onset MS and exacerbations of MS have been seen in post-marketing reports of etanercept and MS is mentioned in the Warning section of the Enbrel label. Apart from the case of MS, no pattern of increased SAEs, grade 3 or 4 AE's or abnormal laboratory values were observed in the placebo-controlled portions of the psoriatic arthritis trials. Overall, the adverse events that were observed in etanercept-treated patients were similar to those seen in patients with rheumatoid arthritis.

Responses to pneumococcal polysaccharide vaccine were measured in psoriatic arthritis patients in study 0030. The proportion of subjects with at least a 2-fold increase in antibody titers to five pneumococcal antigens was similar, but somewhat less, for etanercept-treated patients than placebo-treated patients. In addition, the geometric mean titers were also somewhat less among etanercept-treated patients. An exploratory subset analysis suggested that antibody responses were affected more by concomitant use of methotrexate, by older age and by diabetes than they were by treatment with etanercept.

VI. Financial disclosure

A single clinical investigator reported holdings of Immunex stock that constituted a significant equity interest of $50,000 or greater. That investigator held 2400 shares, with an estimated value of $78,600 as of the closing price on 3/1/2001. Since higher ACR20 responses were observed in etanercept-treated patients in most of the study sites (see section II.C.1 above), the overall results did not depend on any single center. Therefore, it does not appear that financial conflict of interest played an important role in the results seen in this trial.

VII. Conclusions and recommendations

I recommend approval of this BLA supplement. Etanercept should be approved for reducing the signs and symptoms of active arthritis in patients with psoriatic arthritis. Although the skin lesions of psoriasis were also improved in this group of patients, the

[redacted]

[redacted]

The data on B cell antibody responses to pneumococcal polysaccharide vaccination, in combination with previously reported historically controlled data on responses to [redacted] indicate that etanercept treatment is not associated with a large suppression of the ability to respond to vaccination. Nonetheless, some decrease was observed in the magnitude of the responses. The clinical significance of this is unknown. These data indicate that patients receiving etanercept may receive concurrent vaccination, except for live vaccines. The package insert submitted by Immunex on January 14, 2002 contains all requested revisions.